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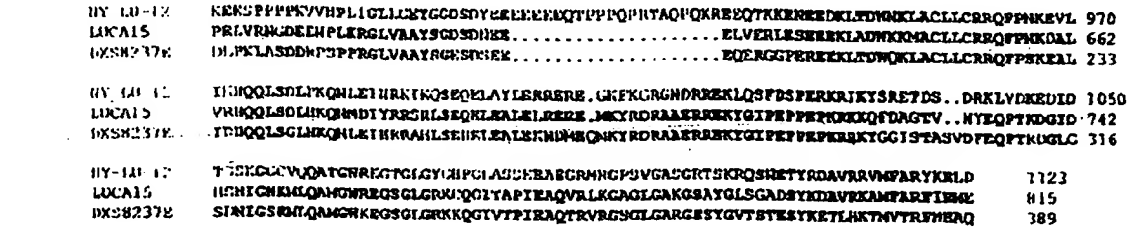

(57) Abstract

Various molecules associated with cancer are disclosed. The invention also discloses diagnostic and therapeutic methods based upon these molecules.

CANCER ASSOCIATED NUCLEIC ACIDS AND POLYPEPTIDES

Field of the Invention

The invention relates to nucleic acids and encoded polypeptides which are cancer associated antigens expressed in patients afflicted with breast cancer. The invention also relates to agents which bind the nucleic acids or polypeptides. The nucleic acid molecules, polypeptides coded for by such molecules and peptides derived therefrom, as well as related antibodies and cytolytic T lymphocytes, are useful, *inter alia*, in diagnostic and therapeutic contexts.

Background of the Invention

The mechanism by which T cells recognize foreign materials has been implicated in cancer. A number of cytolytic T lymphocyte (CTL) clones directed against autologous melanoma antigens, testicular antigens, and melanocyte differentiation antigens have been described. In many instances, the antigens recognized by these clones have been characterized.

The use of autologous CTLs for identifying tumor antigens requires that the target cells which express the antigens can be cultured *in vitro* and that stable lines of autologous CTL clones which recognize the antigen-expressing cells can be isolated and propagated. While this approach has worked well for melanoma antigens, other tumor types, such as epithelial cancers including breast and colon cancer, have proved refractory to the approach.

More recently another approach to the problem has been described by Sahin et al. (*Proc. Natl. Acad. Sci. USA* 92:11810-11813, 1995). According to this approach, autologous antisera are used to identify immunogenic protein antigens expressed in cancer cells by screening expression libraries constructed from tumor cell cDNA. Antigen-encoding clones so identified have been found to have elicited an high-titer humoral immune response in the patients from which the antisera were obtained. Such a high-titer IgG response implies helper T cell recognition of the detected antigen. These tumor antigens can then be screened for the presence of MHC/HLA class I and class II motifs and reactivity with CTLs

The invention is elaborated upon in the disclosure which follows.

Summary of the Invention

Autologous antibody screening has now been applied to cancer using antisera from cancer patients. Numerous cancer associated antigens have been identified. The invention provides, *inter alia*, isolated nucleic acid molecules, expression vectors containing those molecules and host cells transfected with those molecules. The invention also provides isolated proteins and peptides, antibodies to those proteins and peptides and CTLs which recognize the proteins and peptides. Fragments including functional fragments and variants of the foregoing also are provided. Kits containing the foregoing molecules additionally are provided. The foregoing can be used in the diagnosis, monitoring, research, or treatment of conditions characterized by the expression of one or more cancer associated antigens.

Prior to the present invention, only a handful of cancer associated genes had been identified in the past 20 years. The invention involves the surprising discovery of many genes, some previously known and many previously unknown, which are expressed in individuals who have cancer. These individuals all have serum antibodies against the proteins (or fragments thereof) encoded by these genes. Thus, abnormally expressed genes are recognized by the host's immune system and therefore can form a basis for diagnosis, monitoring and therapy.

The invention involves the use of a single material, a plurality of different materials and even large panels and combinations of materials. For example, a single gene, a single protein encoded by a gene, a single functional fragment thereof, a single antibody thereto, etc. can be used in methods and products of the invention. Likewise, pairs, groups and even panels of these materials can be used for diagnosis, monitoring and therapy. The pairs, groups or panels can involve 2, 3, 4, 5... to as many as 25, 50, 100 or more genes, gene products, fragments thereof or agents that recognize such materials. A plurality of such materials are not only useful in monitoring, typing, characterizing and diagnosing cells abnormally expressing such genes, but a plurality of such materials can be used therapeutically. An example of the use of a plurality of such materials for the prevention, delay of onset, amelioration, etc. of cancer cells, which express or will express such genes prophylactically or acutely. Any and all combinations of the genes, gene products, and materials which recognize the genes and gene products can be tested and identified for use according to the invention. It would be far too lengthy to recite all such combinations; those skilled in the art, particularly in view of the teaching contained herein, will readily be able to determine which combinations are most appropriate for which circumstances.

As will be clear from the following discussion, the invention has *in vivo* and *in vitro* uses,

including for therapeutic, diagnostic, monitoring and research purposes. One aspect of the invention is the ability to fingerprint a cell expressing a number of the genes identified according to the invention. Such fingerprints will be characteristic, for example, of the stage of the cancer, the type of the cancer, or even the effect in animal models of a therapy on a cancer. Cells also can be screened to determine whether such cells abnormally express the genes identified according to the invention.

The invention, in one aspect, is a method of diagnosing a disorder characterized by expression of a cancer associated antigen precursor coded for by a nucleic acid molecule. The method involves the steps of contacting a biological sample isolated from a subject with an agent that specifically binds to the nucleic acid molecule, an expression product thereof, or a fragment of an expression product thereof complexed with an MHC, preferably an HLA, molecule, wherein the nucleic acid molecule is a NA Group 1 nucleic acid molecule, and determining the interaction between the agent and the nucleic acid molecule, the expression product or fragment of the expression product as a determination of the disorder.

In one embodiment the agent is selected from the group consisting of (a) a nucleic acid molecule comprising NA Group 1 nucleic acid molecules or a fragment thereof, (b) a nucleic acid molecule comprising NA Group 3 nucleic acid molecules or a fragment thereof, (c) a nucleic acid molecule comprising NA Group 17 nucleic acid molecules or a fragment thereof, (d) an antibody that binds to an expression product, or a fragment thereof, of NA group 1 nucleic acids, (e) an antibody that binds to an expression product, or a fragment thereof, of NA group 3 nucleic acids, (f) an antibody that binds to an expression product, or a fragment thereof, of NA group 17 nucleic acids, (g) and agent that binds to a complex of an MHC, preferably HLA, molecule and a fragment of an expression product of a NA Group 1 nucleic acid, (h) an agent that binds to a complex of an MHC, preferably HLA, molecule and a fragment of an expression product of a NA group 3 nucleic acid, and (I) an agent that binds to a complex of an MHC, preferably HLA, molecule and a fragment of an expression product of a NA Group 17 nucleic acid.

The disorder may be characterized by expression of a plurality of cancer associated antigen precursors and wherein the agent is a plurality of agents, each of which is specific for a different human cancer associated antigen precursor, and wherein said plurality of agents is at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9 or at least 10 such agents.

In each of the above embodiments the agent may be specific for a human cancer associated antigen precursor that is a breast, a gastric, a lung, a prostate, a renal or a colon cancer associated antigen precursor.

In another aspect the invention is a method for determining regression, progression or onset of a condition characterized by expression of abnormal levels of a protein encoded by a nucleic acid molecule that is a NA Group 1 molecule. The method involves the steps of monitoring a sample, from a subject who has or is suspected of having the condition, for a parameter selected from the group consisting of (i) the protein, (ii) a peptide derived from the protein, (iii) an antibody which selectively binds the protein or peptide, and (iv) cytolytic T cells specific for a complex of the peptide derived from the protein and an MHC molecule, as a determination of regression, progression or onset of said condition. In one embodiment the sample is a body fluid, a body effusion or a tissue.

In another embodiment the step of monitoring comprises contacting the sample with a detectable agent selected from the group consisting of (a) an antibody which selectively binds the protein of (i), or the peptide of (ii), (b) a protein or peptide which binds the antibody of (iii), and (c) a cell which presents the complex of the peptide and MHC molecule of (iv). In a preferred embodiment the antibody, the protein, the peptide or the cell is labeled with a radioactive label or an enzyme. The sample in a preferred embodiment is assayed for the peptide.

According to another embodiment the nucleic acid molecule is one of the following: a NA Group 3 molecule, a NA Group 11 molecule, a NA Group 12 molecule, a NA Group 13 molecule, a NA Group 14 molecule, a NA Group 15 molecule, or a NA Group 16 molecule. In yet another embodiment the protein is a plurality of proteins, the parameter is a plurality of parameters, each of the plurality of parameters being specific for a different of the plurality of proteins.

The invention in another aspect is a pharmaceutical preparation for a human subject. The pharmaceutical preparation includes an agent which when administered to the subject enriches selectively the presence of complexes of an HLA molecule and a human cancer associated antigen, and a pharmaceutically acceptable carrier, wherein the human cancer associated antigen is a fragment of a human cancer associated antigen precursor encoded by a nucleic acid molecule which comprises a NA Group 1 molecule. In one embodiment the nucleic acid molecule is a NA Group 3 nucleic acid molecule.

The agent in one embodiment comprises a plurality of agents, each of which enriches selectively in the subject complexes of an HLA molecule and a different human cancer associated antigen. Preferably the plurality is at least two, at least three, at least four or at least 5 different such agents.

In another embodiment the agent is selected from the group consisting of (1) an isolated polypeptide comprising the human cancer associated antigen, or a functional variant thereof, (2) an isolated nucleic acid operably linked to a promoter for expressing the isolated polypeptide, or functional variant thereof, (3) a host cell expressing the isolated polypeptide, or functional variant thereof, and (4) isolated complexes of the polypeptide, or functional variant thereof, and an HLA molecule.

The agent may be a cell expressing an isolated polypeptide. In one embodiment the agent is a cell expressing an isolated polypeptide comprising the human cancer associated antigen or a functional variant thereof, and wherein the cell is nonproliferative. In another embodiment the agent is a cell expressing an isolated polypeptide comprising the human cancer associated antigen or a functional variant thereof, and wherein the cell expresses an HLA molecule that binds the polypeptide. The cell can express one or both of the polypeptide and HLA molecule recombinantly. In another preferred embodiment the cell is nonproliferative. In yet another embodiment the agent is at least two, at least three, at least four or at least five different polypeptides, each representing a different human cancer associated antigen or functional variant thereof.

The agent in one embodiment is a PP Group 2 polypeptide. In other embodiments the agent is a PP Group 3 polypeptide or a PP Group 4 polypeptide.

In an embodiment each of the pharmaceutical preparations described herein also includes an adjuvant.

According to another aspect the invention, a composition is provided of an isolated agent that binds selectively a PP Group 1 polypeptide. In separate embodiments the agent binds selectively to a polypeptide selected from the following: a PP Group 3 polypeptide, a PP Group 11 polypeptide, a PP Group 12 polypeptide, a PP Group 13 polypeptide, a PP Group 14 polypeptide, a PP Group 15 polypeptide, and a PP Group 16 polypeptide. In other embodiments, the agent is a plurality of different agents that bind selectively at least two, at least three, at least four, or at least five different such polypeptides. In each of the above described embodiments the agent may be an antibody.

In another aspect the invention is a composition of matter .composed of a conjugate of the agent of the above-described compositions of the invention and a therapeutic or diagnostic agent. Preferably the conjugate is of the agent and a therapeutic or diagnostic that is an antineoplastic.

The invention in another aspect is a pharmaceutical composition of an isolated nucleic acid molecule selected from the group consisting of: (1) NA Group 1 molecules, and (2) NA Group 2 molecules, and a pharmaceutically acceptable carrier. In one embodiment the isolated nucleic acid molecule comprises a NA Group 3 or NA Group 4 molecule. In another embodiment the isolated nucleic acid molecule comprises at least two isolated nucleic acid molecules coding for two different polypeptides, each polypeptide comprising a different cancer associated antigen.

Preferably the pharmaceutical composition also includes an expression vector with a promoter operably linked to the isolated nucleic acid molecule. In another embodiment the pharmaceutical composition also includes a host cell recombinantly expressing the isolated nucleic acid molecule.

According to another aspect of the invention a pharmaceutical composition is provided. The pharmaceutical composition includes an isolated polypeptide comprising a PP Group 1 or a PP Group 2 polypeptide, and a pharmaceutically acceptable carrier. In one embodiment the isolated polypeptide comprises a PP Group 3 or a PP Group 4 polypeptide.

In another embodiment the isolated polypeptide comprises at least two different polypeptides, each comprising a different cancer associated antigen. In separate embodiments the isolated polypeptides are selected from the following: PP Group 11 polypeptides or HLA binding fragments thereof, PP Group 12 polypeptides or HLA binding fragments thereof, PP Group 13 polypeptides or HLA binding fragments thereof, PP Group 14 polypeptides or HLA binding fragments thereof, PP Group 15 polypeptides or HLA binding fragments thereof, or PP Group 16 polypeptides or HLA binding fragments thereof.

In an embodiment each of the pharmaceutical compositions described herein also includes an adjuvant.

Another aspect the invention is an isolated nucleic acid molecule comprising a NA Group 3 molecule. Another aspect the invention is an isolated nucleic acid molecule comprising a NA Group 4 molecule. In separate embodiments the isolated nucleic acid molecules are selected from the following: a Group 11 molecule or a functional fragment

thereof, a Group 12 molecule or a functional fragment thereof, a Group 13 molecule or a functional fragment thereof, a Group 14 molecule or a functional fragment thereof, a Group 15 molecule or a functional fragment thereof, or a Group 16 molecule or a functional fragment thereof.

The invention in another aspect is an isolated nucleic acid molecule selected from the group consisting of (a) a fragment of a nucleic acid selected from the group of nucleic acid molecules consisting of SEQ ID numbered below and comprising all nucleic acid sequences among SEQ ID NOs 1-816, of sufficient length to represent a sequence unique within the human genome, and identifying a nucleic acid encoding a human cancer associated antigen precursor, (b) complements of (a), provided that the fragment includes a sequence of contiguous nucleotides which is not identical to any sequence selected from the sequence group consisting of (1) sequences having the GenBank accession numbers of the sequence Group 1, (2) complements of (1), and (3) fragments of (1) and (2).

In one embodiment the sequence of contiguous nucleotides is selected from the group consisting of: (1) at least two contiguous nucleotides nonidentical to the sequence Group 1, (2) at least three contiguous nucleotides nonidentical to the sequence Group 1, (3) at least four contiguous nucleotides nonidentical to the sequence Group 1, (4) at least five contiguous nucleotides nonidentical to the sequence Group 1, (5) at least six contiguous nucleotides nonidentical to the sequence Group 1, or (6) at least seven contiguous nucleotides nonidentical to the sequence Group 1.

In another embodiment the fragment has a size selected from the group consisting of at least: 8 nucleotides, 10 nucleotides, 12 nucleotides, 14 nucleotides, 16 nucleotides, 18 nucleotides, 20, nucleotides, 22 nucleotides, 24 nucleotides, 26 nucleotides, 28 nucleotides, 30 nucleotides, 50 nucleotides, 75 nucleotides, 100 nucleotides, 200 nucleotides, 1000 nucleotides and every integer length therebetween.

In yet another embodiment the molecule encodes a polypeptide which, or a fragment of which, binds a human HLA receptor or a human antibody.

Another aspect of the invention is an expression vector comprising an isolated nucleic acid molecule of the invention described above operably linked to a promoter.

According to one aspect the invention is an expression vector comprising a nucleic acid operably linked to a promoter, wherein the nucleic acid is a NA Group 2 molecule. In another aspect the invention is an expression vector comprising a NA Group 1 or Group 2 molecule

1. A method of diagnosing a disorder characterized by expression of a human cancer associated antigen precursor coded for by a nucleic acid molecule, comprising:

contacting a biological sample isolated from a subject with an agent that specifically binds to the nucleic acid molecule, an expression product thereof, or a fragment of an expression product thereof complexed with an HLA molecule, wherein the nucleic acid molecule is a NA Group 1 nucleic acid molecule, and

determining the interaction between the agent and the nucleic acid molecule or the expression product as a determination of the disorder.

2. The method of claim 1, wherein the agent is selected from the group consisting of

(a)

a nucleotide acid molecule comprising NA group 1 nucleic acid molecules or a fragment thereof,

(b)

a nucleic acid molecule comprising NA group 3 nucleic acid molecules or a fragment thereof,

(c)

a nucleic acid molecule comprising NA group 17 nucleic acid molecules or a fragment thereof,

(d)

an antibody that binds to an expression product of NA group 1 nucleic acids,

(e)

an antibody that binds to an expression product of NA group 3 nucleic acids,

(f)

an antibody that binds to an expression product of NA group 17 nucleic acids,

(g)

and agent that binds to a complex of an HLA molecule and a fragment of an expression product of a NA group 1 nucleic acid,

(h)

an agent that binds to a complex of an HLA molecule and a fragment of an expression product of a NA group 3 nucleic acid, and

(I)

an agent that binds to a complex of an HLA molecule and a fragment of an expression product of a NA group 17 nucleic acid.

3. The method of claim 1, wherein the disorder is characterized by expression of a plurality of human cancer associated antigen precursors and wherein the agent is a plurality of agents, each of which is specific for a different human cancer associated antigen precursor, and wherein said plurality of agents is at least 2, at least 3, at least 4, at least 4, at least 6, at least 7, or at least 8, at least 9 or at least 10 such agents.

4. The method of claims 1-3, wherein the agent is specific for a human cancer associated antigen precursor that is a breast, a gastric, a lung, a prostate, a renal or a colon cancer associated antigen precursor.

5. A method for determining regression, progression or onset of a condition characterized by expression of abnormal levels of a protein encoded by a nucleic acid molecule that is a NA Group 1 molecule, comprising

monitoring a sample, from a patient who has or is suspected of having the condition, for a parameter selected from the group consisting of

(I)

the protein,

(ii)

a peptide derived from the protein,

(iii)

an antibody which selectively binds the protein or peptide, and

(iv)

cytolytic T cells specific for a complex of the peptide derived from the protein and an MHC molecule,

as a determination of regression, progression or onset of said condition.

6. The method of claim 5, wherein the sample is a body fluid, a body effusion or a tissue.

7. The method of claim 5, wherein the step of monitoring comprises contacting the sample with a detectable agent selected from the group consisting of

(a)

an antibody which selectively binds the protein of (I), or the peptide of (ii),

(b)

a protein or peptide which binds the antibody of (iii), and

(c)

a cell which presents the complex of the peptide and MHC molecule of (iv).

8. The method of claim 7, wherein the antibody, the protein, the peptide or the cell is labeled with a radioactive label or an enzyme.

9. The method of claim 5, comprising assaying the sample for the peptide.

10. The method of claim 5, wherein the nucleic acid molecule is a NA Group 3 molecule.

11. The method of claim 5, wherein the nucleic acid molecule is a NA Group 11 molecule.

12. The method of claim 5, wherein the nucleic acid molecule is a NA Group 12 molecule.

13. The method of claim 5, wherein the nucleic acid molecule is a NA Group 13 molecule.

14. The method of claim 5, wherein the nucleic acid molecule is a NA Group 14 molecule.

15. The method of claim 5, wherein the nucleic acid molecule is a NA Group 15 molecule.

16. The method of claim 5, wherein the nucleic acid molecule is a NA Group 16 molecule.

17. The method of claim 5, wherein the protein is a plurality of proteins, the parameter is a plurality of parameters, each of the plurality of parameters being specific for a different of the plurality of proteins.

18. A pharmaceutical preparation for a human subject comprising

an agent which when administered to the subject enriches selectively the presence of complexes of an HLA molecule and a human cancer associated antigen, and

a pharmaceutically acceptable carrier, wherein the human cancer associated antigen is a fragment of a human cancer associated antigen precursor encoded by a nucleic acid molecule comprises a NA Group 1 molecule.

19. The pharmaceutical preparation of claim 18, wherein the agent comprises a plurality of agents, each of which enriches selectively in the subject complexes of an HLA molecule and a different human cancer associated antigen.

20. The pharmaceutical preparation of claim 19, wherein the plurality is at least two, at least three, at least four or at least 5 different such agents.

21. The pharmaceutical preparation of claim 18, wherein the nucleic acid molecule is a NA Group 3 nucleic acid molecule.

22. The pharmaceutical preparation of claim 18, wherein the agent is selected from the group consisting of

(1) an isolated polypeptide comprising the human cancer associated antigen, or a functional variant thereof,

(2) an isolated nucleic acid operably linked to a promoter for expressing the isolated polypeptide, or functional variant thereof,

(3) a host cell expressing the isolated polypeptide, or functional variant thereof, and

(4) isolated complexes of the polypeptide, or functional variant thereof, and an HLA molecule.

23. The pharmaceutical preparation of claims 18-22, further comprising an adjuvant.

24. The pharmaceutical preparation of claim 18, wherein the agent is a cell expressing an isolated polypeptide comprising the human cancer associated antigen or a functional variant thereof, and wherein the cell is nonproliferative.

25. The pharmaceutical preparation of claim 18, wherein the agent is a cell expressing an isolated polypeptide comprising the human cancer associated antigen or a functional variant thereof, and wherein the cell expresses an HLA molecule that binds the polypeptide.

26. The pharmaceutical preparation of claim 18, wherein the agent is at least two, at least three, at least four or at least five different polypeptides, each coding for a different human cancer associated antigen or functional variant thereof.

27. The pharmaceutical preparation of claim 18, wherein the agent is a PP Group 2 polypeptide.

28. The pharmaceutical preparation of claim 18, wherein the agent is a PP Group 3 polypeptide or a PP Group 4 polypeptide.

29. The pharmaceutical preparation of claim 25, wherein the cell expresses one or both of the polypeptide and HLA molecule recombinantly.

30. The pharmaceutical preparation of claim 25, wherein the cell is nonproliferative.

31. A composition comprising
an isolated agent that binds selectively a PP Group 1 polypeptide.

32. The composition of matter of claim 31, wherein the agent binds selectively a PP Group 3 polypeptide.

33. The composition of matter of claim 31, wherein the agent binds selectively a PP Group 11 polypeptide.

34. The composition of matter of claim 31, wherein the agent binds selectively a PP Group 12 polypeptide.

35. The composition of matter of claim 31, wherein the agent binds selectively a PP Group 13 polypeptide.

36. The composition of matter of claim 31, wherein the agent binds selectively a PP Group 14 polypeptide.

37. The composition of matter of claim 31, wherein the agent binds selectively a PP Group 15 polypeptide.

38. The composition of matter of claim 31, wherein the agent binds selectively a PP Group 16 polypeptide.

39. The composition of claims 31-38, wherein the agent is a plurality of different agents that bind selectively at least two, at least three, at least four, or at least five different such polypeptides.

40. The composition of claims 31-38, wherein the agent is an antibody.

41. The composition of claim 39, wherein the agent is an antibody.

42. A composition of matter comprising
a conjugate of the agent of claims 31-41 and a therapeutic or diagnostic agent.

43. The composition of matter of claim 42, wherein the conjugate is of the agent and a therapeutic or diagnostic that is a toxin.

44. A pharmaceutical composition comprising an isolated nucleic acid molecule selected from the group consisting of:
(1)
NA Group 1 molecules, and
(2)
NA Group 2 molecules, and a pharmaceutically acceptable carrier.

45. The pharmaceutical composition of claim 44, wherein the isolated nucleic acid molecule comprises a NA Group 3 or NA Group 4 molecule.

46. The pharmaceutical composition of claim 44, wherein the isolated nucleic acid molecule comprises at least two isolated nucleic acid molecules coding for two different polypeptides, each polypeptide comprising a different human cancer associated antigen.

47. The pharmaceutical composition of claims 44-46 further comprising an expression vector with a promoter operably linked to the isolated nucleic acid molecule.

48. The pharmaceutical composition of claims 44-46 further comprising a host cell recombinantly expressing the isolated nucleic acid molecule.

49. A pharmaceutical composition comprising

an isolated polypeptide comprising a PP Group 1 or a PP Group 2 polypeptide, and

a pharmaceutically acceptable carrier.

50. The pharmaceutical composition of claim 49, wherein the isolated polypeptide comprises a PP Group 3 or a PP Group 4 polypeptide.

51. The pharmaceutical composition of claim 49, wherein the isolated polypeptide comprises at least two different polypeptides, each comprising a different human cancer associated antigen.

52. The pharmaceutical composition of claim 49, wherein the isolated polypeptides are PP Group 11 polypeptides or HLA binding fragments thereof.

53. The pharmaceutical composition of claim 49, wherein the isolated polypeptides are PP
Group 12 polypeptides or HLA binding fragments thereof.

54. The pharmaceutical composition of claim 49, wherein the isolated polypeptides are PP Group 13 polypeptides or HLA binding fragments thereof.

55. The pharmaceutical composition of claim 49, wherein the isolated polypeptides are PP Group 14 polypeptides or HLA binding fragments thereof.

56. The pharmaceutical composition of claim 49, wherein the isolated polypeptides are PP Group 15 polypeptides or HLA binding fragments thereof.

57. The pharmaceutical composition of claim 49, wherein the isolated polypeptides are PP Group 16 polypeptides or HLA binding fragments thereof.

58. The pharmaceutical composition of claims 49-57, further comprising an adjuvant.

59. An isolated nucleic acid molecule comprising a NA Group 3 molecule.

60. An isolated nucleic acid molecule comprising a NA Group 4 molecule.

61. The isolated nucleic acid molecule of claims 59-60, wherein the molecule is a Group 11 molecule or a fragment thereof.

62. The isolated nucleic acid molecule of claims 59-60, wherein the molecule is a Group 12 molecule or a fragment thereof.

63. The isolated nucleic acid molecule of claims 59-60, wherein the molecule is a Group 13 molecule or a fragment thereof.

64. The isolated nucleic acid molecule of claims 59-60, wherein the molecule is a Group 14 molecule or a fragment thereof.

65. The isolated nucleic acid molecule of claims 59-60, wherein the molecule is a Group 15 molecule or a fragment thereof.

66. The isolated nucleic acid molecule of claims 59-60, wherein the molecule is a Group 16 molecule or a fragment thereof.

67. An isolated nucleic acid molecule selected from the group consisting of

(a)

a fragment of a nucleic acid selected from the group of nucleic acid consisting of SEQ ID NOs presenting nucleic acid sequences among SEQ ID NOs. 1-816, of sufficient length to represent a sequence unique within the human genome, and identifying a nucleic acid encoding a human cancer associated antigen precursor,

(b)

complements of (a),

provided that the fragment includes a sequence of contiguous nucleotides which is not identical to any sequence selected from the sequence group consisting of

(1) sequences having the GenBank accession numbers of Table 1 (**correct?**),

(2) complements of (1), and

(3) fragments of (1) and (2).

68. The isolated nucleic acid molecule of claim 67, wherein the sequence of contiguous nucleotides is selected from the group consisting of:

(1)

at least two contiguous nucleotides nonidentical to the sequence group,

(2)

at least three contiguous nucleotides nonidentical to the sequence group,

(3)

at least four contiguous nucleotides nonidentical to the sequence group,

(4)

at least five contiguous nucleotides nonidentical to the sequence group,

(5)

at least six contiguous nucleotides nonidentical to the sequence group,

(6)

at least seven contiguous nucleotides nonidentical to the sequence group.

69. The isolated nucleic acid molecule of claim 67, wherein the fragment has a size selected from the group consisting of at least: 8 nucleotides, 10 nucleotides, 12 nucleotides, 14 nucleotides, 16 nucleotides, 18 nucleotides, 20, nucleotides, 22 nucleotides, 24 nucleotides, 26 nucleotides, 28 nucleotides, 30 nucleotides, 50 nucleotides, 75 nucleotides, 100 nucleotides, and 200 nucleotides.

70. The isolated nucleic acid molecule of claim 67, wherein the molecule encodes a polypeptide which, or a fragment of which, binds a human HLA receptor or a human antibody.

71. An expression vector comprising an isolated nucleic acid molecule of claims 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69 or 70 operably linked to a promoter.

72. An expression vector comprising a nucleic acid operably linked to a promoter, wherein the nucleic acid is a NA Group 2 molecule.

73. An expression vector comprising a NA Group 1 or Group 2 molecule and a nucleic acid encoding an HLA molecule.

74. A host cell transformed or transfected with an expression vector of claims 71, 72, or 73.

75. A host cell transformed or transfected with an expression vector of claim 71 or claim 72 and further comprising a nucleic acid encoding HLA.

76. An isolated polypeptide encoded by the isolated nucleic acid molecule of claims 59, 60, 61, 62, 63, 64, 65, or 66.

77. A fragment of the polypeptide of claim 76 which is immunogenic.

78. The fragment of claim 77, wherein the fragment, or a portion of the fragment, binds HLA or a human antibody.

79. An isolated fragment of a human cancer associated antigen precursor which, or portion of which, binds HLA or a human antibody, wherein the precursor is encoded by a nucleic acid molecule that is a NA Group 1 molecule.

80. The fragment of claim 79, wherein the fragment is part of a complex with HLA.

81. The fragment of claim 79, wherein the fragment is between 8 and 12 amino acids in length.

82. An isolated polypeptide comprising a fragment of the polypeptide of claim 76 of sufficient length to represent a sequence unique within the human genome and identifying a polypeptide that is a human cancer associated antigen precursor.

83. A kit for detecting the presence of the expression of a human cancer associated antigen precursor comprising

a pair of isolated nucleic acid molecules each of which consists essentially of a molecule selected from the group consisting of

(a) a 12-32 nucleotide contiguous segment of the nucleotide sequence of any of the NA Group 1 molecules and

(b) complements of ("a"), wherein the contiguous segments are nonoverlapping.

84. The kit of claim 83, wherein the pair of isolated nucleic acid molecules is constructed and arranged to selectively amplify an isolated nucleic acid molecule that is a NA Group 3 molecule.

85. A method for treating a subject with a disorder characterized by expression of a human cancer associated antigen precursor, comprising

administering to the subject an amount of an agent, which enriches selectively in the subject the presence of complexes of an HLA molecule and a human cancer associated antigen, effective to ameliorate the disorder, wherein the human cancer associated antigen is a fragment of a human cancer associated antigen precursor encoded by a nucleic acid molecule selected from the group consisting of

(a)

a nucleic acid molecule comprising NA group 1 nucleic acid molecules,

(b)

a nucleic acid molecule comprising NA group 3 nucleic acid molecules,

(c)

a nucleic acid molecule comprising NA group 17 nucleic acid molecules.

86. The method of claim 85, wherein the disorder is characterized by expression of a plurality of human cancer associated antigen precursors and wherein the agent is a plurality of agents, each of which enriches selectively in the subject the presence of complexes of an HLA molecule and a different human cancer associated antigen.

87. The method of claim 86, wherein the plurality is at least 2, at least 3, at least 4, or at least 5 such agents.

88. The method of claims 85-87, wherein the agent is an isolated polypeptide selected from the group consisting of PP Group 1, PP Group 2, PP Group 3, PP Group 4, PP Group 5, PP Group 6, PP Group 7, PP Group 8, PP Group 9, PP Group 10, PP Group 11, PP Group 12, PP Group 13, PP Group 14, PP Group 15, PP Group 16 and PP Group 17 polypeptides.

89. The method of claims 85-88, wherein the disorder is cancer.

90. A method for treating a subject having a condition characterized by expression of a human cancer associated antigen precursor in cells of the subject, comprising:

(I)

removing an immunoreactive cell containing sample from the subject,

(ii)

contacting the immunoreactive cell containing sample to the host cell under conditions favoring production of cytolytic T cells against a human cancer associated antigen which is a fragment of the precursor,

(iii)

introducing the cytolytic T cells to the subject in an amount effective to lyse cells which express the human cancer associated antigen, wherein the host cell is transformed or transfected with an expression vector comprising an isolated nucleic acid molecule operably linked to a promoter, the isolated nucleic acid molecule being selected from the group of nucleic acid molecules consisting of NA Group 1, NA Group 2, NA Group 3, NA Group 4, NA Group 5, NA Group 6, NA Group 7, NA Group 8, NA Group 9, NA Group 10, NA Group 11, NA Group 12, NA Group 13, NA Group 14, NA Group 15, NA Group 16, and NA Group 17.

91. The method of claim 90, wherein the host cell recombinantly expresses an HLA molecule which binds the human cancer associated antigen.

92. The method of claim 90, wherein the host cell endogenously expresses an HLA molecule which binds the human cancer associated antigen.

93. A method for treating a subject having a condition characterized by expression of a human cancer associated antigen precursor in cells of the subject, comprising:

(I)

identifying a nucleic acid molecule expressed by the cells associated with said condition, wherein said nucleic acid molecule is a NA Group 1 molecule

(ii)

transfecting a host cell with a nucleic acid selected from the group consisting of

(a) the nucleic acid molecule identified,

(b)

a fragment of the nucleic acid identified which includes a segment coding for a human cancer associated antigen,

(c)

deletions, substitutions or additions to (a) or (b), and

(d)

degenerates of (a), (b), or (c);

(iii)

culturing said transfected host cells to express the transfected nucleic acid molecule, and;

(iv)

introducing an amount of said host cells or an extract thereof to the subject effective to increase an immune response against the cells of the subject associated with the condition.

94. The method of claim 93, further comprising:

(a)

identifying an MHC molecule which presents a portion of an expression product of the nucleic acid molecule,

wherein the host cell expresses the same MHC molecule as identified in (a) and wherein the host cell presents an MHC binding portion of the expression product of the nucleic acid molecule.

95. The method of claim 93, wherein the immune response comprises a B-cell response or a T cell response.

96. The method of claim 95, wherein the response is a T-cell response which comprises generation of cytolytic T-cells specific for the host cells presenting the portion of the expression product of the nucleic acid molecule or cells of the subject expressing the human cancer associated antigen.

97. The method of claim 93, wherein the nucleic acid molecule is a NA Group 3 molecule.

98. The method of claims 93 or 94, further comprising treating the host cells to render them non-proliferative.

99. A method for treating or diagnosing or monitoring a subject having a condition characterized by expression of an abnormal amount of a protein encoded by a nucleic acid molecule that is a NA Group 1 molecule, comprising

administering to the subject an antibody which specifically binds to the protein or a peptide derived therefrom, the antibody being coupled to a therapeutically useful agent, in an amount effective to treat the condition.

100. The method of claim 99, wherein the antibody is a monoclonal antibody.

101. The method of claim 100, wherein the monoclonal antibody is a chimeric antibody or a humanized antibody.

102. A method for treating a condition characterized by expression in a subject of abnormal amounts of a protein encoded by a nucleic acid molecule that is a NA Group 1 nucleic acid molecule, comprising

administering to a subject a pharmaceutical composition of any one of claims 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 47, and 58 in an amount effective to prevent, delay the onset of, or inhibit the condition in the subject.

103. The method of claim 102, wherein the condition is cancer.

104. The method of claims 102-103, further comprising first identifying that the subject expresses in a tissue abnormal amounts of the protein.

105. A method for treating a subject having a condition characterized by expression of abnormal amounts of a protein encoded by a nucleic acid molecule that is a NA Group 1 nucleic acid molecule, comprising

(I) identifying cells from the subject which express abnormal amounts of the protein;

(ii) isolating a sample of the cells;

(iii) cultivating the cells, and

(iv) introducing the cells to the subject in an amount effective to provoke an immune response against the cells.

106. The method of claim 105, wherein the cells express a protein selected from the group
consisting of a PP Group 11 protein, a PP Group 12 protein, a PP Group 13 protein, PP Group 14 protein, a PP Group 15 protein and a PP Group 16 protein.

107. The method of claim 105, further comprising rendering the cells non-proliferative, prior to introducing them to the subject.

108. A method for treating a pathological cell condition characterized by aberrant expression of a protein encoded by a nucleic acid molecule that is a NA Group 1 nucleic acid molecule, comprising

administering to a subject in need thereof an effective amount of an agent which inhibits the expression or activity of the protein.

109. The method of claim 108, wherein the agent is an inhibiting antibody which selectively binds to the protein and wherein the antibody is a monoclonal antibody, a chimeric antibody or a humanized antibody.

110. The method of claim 108, wherein the agent is an antisense nucleic acid molecule which selectively binds to the nucleic acid molecule which encodes the protein.

111. The method of claim 108, wherein the nucleic acid molecule is a NA Group 3 nucleic acid molecule.

112. A composition of matter useful in stimulating an immune response to a plurality of a protein encoded by nucleic acid molecules that are NA Group 1 molecules, comprising

a plurality of peptides derived from the amino acid sequences of the proteins, wherein the peptides bind to one or more MHC molecules presented on the surface of the cells which express an abnormal amount of the protein.

113. The composition of matter of claim 112, wherein at least a portion of the plurality of peptides bind to MHC molecules and elicit a cytolytic response thereto.

114. The composition of matter of claim 113, further comprising an adjuvant.

115. The composition of matter of claim 114, wherein said adjuvant is a saponin, GM-CSF, or an interleukin.

116. An isolated antibody which selectively binds to a complex of:

(i)

a peptide derived from a protein encoded by a nucleic acid molecule that is a NA Group 1 molecule and

(ii)

and an MHC molecule to which binds the peptide to form the complex, wherein the isolated antibody does not bind to (I) or (ii) alone.

117. The antibody of claim 116, wherein the antibody is a monoclonal antibody, a chimeric antibody or a humanized antibody.

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